

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year)

17 October 1996 (17.10.96)

International application No.

PCT/GB96/00575

Applicant's or agent's file reference

MBUS 1126A PCT

International filing date (day/month/year)

19 March 1996 (19.03.96)

Priority date (day/month/year)

25 March 1995 (25.03.95)

Applicant

MURRER, Barry, Anthony et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

30 September 1996 (30.09.96)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Authorized officer

Peggy Steunenberg

# PATENT COOPERATION TREATY

RECEIVED  
23 MAY 1997

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

WISHART, Ian C.  
JOHNSON MATTHEY plc.  
Technology Centre  
Blounts Court  
Sonning Common  
Reading RG4 9NH  
GRANDE BRETAGNE

## NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing  
(day/month/year)

20.05.97

Applicant's or agent's file reference

MBUS 1126A PCT

### IMPORTANT NOTIFICATION

International application No.

PCT/GB 96/ 00575

International filing date (day/month/year)

19/03/1996

Priority date (day/month/year)

25/03/1995

Applicant

JOHNSON MATTHEY PUBLIC LIMITED COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



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Ben Thlija

# PATENT COOPERATION TREATY

# PCT


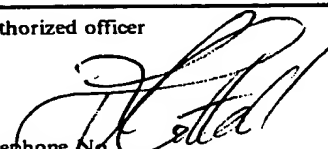
## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>MBUS 1126A PCT</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/GB 96/ 00575</b>	International filing date ( <i>day/month/year</i> ) <b>19/03/1996</b>	Priority date ( <i>day/month/year</i> ) <b>25/03/1995</b>
International Patent Classification (IPC) or national classification and IPC <p style="text-align: center;"><b>A61K33/24</b></p>		
Applicant <b>JOHNSON MATTHEY PUBLIC LIMITED COMPANY et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This **REPORT** consists of a total of   3   sheets, including this cover sheet.
- ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consists of a total of   1   sheets.

3. This report contains indications and corresponding pages relating to the following items:
- I ☒ Basis of the report
  - II ☐ Priority
  - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application

Date of submission of the demand <b>30/09/1996</b>	Date of completion of this report <b>20.05.97</b>
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+ 49-89) 2399-0, Tx: 523656 epmu d Fax: (+ 49-89) 2399-4465	Authorized officer  Telephone No. <b>Cattell</b>

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

## 1. STATEMENT

Novelty (N)	Claims 1-8 _____	YES
	Claims 9 _____	NO
Inventive Step (IS)	Claims 1-6 _____	YES
	Claims 7, 8 _____	NO
Industrial Applicability (IA)	Claims 1-9 _____	YES
	Claims _____	NO

## 2. CITATIONS AND EXPLANATIONS

- 1). Document D1 (Naohisa et al 1991) discloses on page 22 Table 2  $\text{La}_2(\text{CO}_3)_3 \cdot 5\text{H}_2\text{O}$ .  
Document D2 (Chem abs; 107-249009) discloses  $\text{La}_2(\text{CO}_3)_3 \cdot 3\text{H}_2\text{O}$ , as does Document D4 (Chem abs, 87-161013)  
Document D3 (Chem abs; 104-236218) discloses  $\text{La}_2(\text{CO}_3)_3 \cdot 6\text{H}_2\text{O}$ .  
These compounds fall within the scope of claim 9 under Article 33(2) PCT
- 2). D3 describes the preparation of La carbonate by reacting the nitrate with an alkali metal carbonate.  
This disclosure would seem to render the reaction of claims 7 and 8 obvious under Article 33(3) PCT.
- 3). None of the cited documents indicate a pharmaceutical use of the claimed compounds, which is superior to the known forms of carbonate (see description Table 19  
claims 1 to 6 would therefore appear to meet the requirements of Article 33 PCT.

**INTERNATIONAL PRELIMINARY EXAMINATION REPORT****I. Basis of the report**

1. This report has been drawn up on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

☐ the international application as originally filed.

☒ the description, pages 1-13 \_\_\_\_\_, as originally filed,  
pages \_\_\_\_\_, filed with the demand,  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_,

☒ the claims, Nos. 1-6 \_\_\_\_\_, as originally filed,  
Nos. \_\_\_\_\_, as amended under Article 19,  
Nos. \_\_\_\_\_, filed with the demand,  
Nos. 7-9 \_\_\_\_\_, filed with the letter of 12.02.97,  
Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_,

☒ the drawings, sheets/fig 1-4 \_\_\_\_\_, as originally filed,  
sheets/fig \_\_\_\_\_, filed with the demand,  
sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of:

☐ the description, pages \_\_\_\_\_.  
☐ the claims, Nos. \_\_\_\_\_.  
☐ the drawings, sheets/fig \_\_\_\_\_.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT


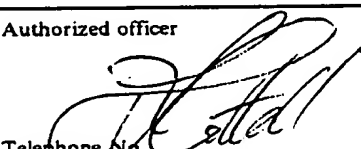
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>MBUS 1126A PCT</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/GB 96/ 00575</b>	International filing date (day/month/year) <b>19/03/1996</b>	Priority date (day/month/year) <b>25/03/1995</b>
International Patent Classification (IPC) or national classification and IPC <b>A61K33/24</b>		
Applicant <b>JOHNSON MATTHEY PUBLIC LIMITED COMPANY et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This **REPORT** consists of a total of 3 sheets, including this cover sheet.
- ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of 1 sheets.

3. This report contains indications and corresponding pages relating to the following items:
- I ☒ Basis of the report
  - II ☐ Priority
  - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application

Date of submission of the demand <b>30/09/1996</b>	Date of completion of this report <b>20.05.97</b>
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer  Telephone No. <b>J. Cattell</b>

*Replaced  
by Art. 34  
Amended*

7. A process for the preparation of lanthanum carbonate as defined in any one of claims 1 to 3 which comprises the steps of:

(i) reacting lanthanum oxide with an acid which gives a soluble salt of lanthanum;

(ii) reacting a solution of the thus obtained lanthanum salt with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and

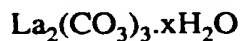
(iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

8. A process as claimed in claim 7 wherein the acid is nitric acid or hydrochloric acid.

9. A process as claimed in claim 7 or 8 wherein the alkali metal carbonate is sodium carbonate.

10. Lanthanum carbonate prepared according to the process of any of claims 7, 8 or 9.

11. Lanthanum carbonate of the formula



where x has a value from 3 to 6.

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## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>MBUS 1126A PCT</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB96/00575</b>	International filing date (day/month/year) <b>19/03/96</b>	(Earliest) Priority Date (day/month/year) <b>25/03/95</b>
Applicant <b>JOHNSON MATTHEY PUBLIC LIMITED COMPANY et al.</b>		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).
2. ☐ Unity of invention is lacking (see Box II).
3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
  - ☐ filed with the international application.
  - ☐ furnished by the applicant separately from the international application,
    - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
  - ☐ Transcribed by this Authority
4. With regard to the title,
  - ☐ the text is approved as submitted by the applicant.
  - ☒ the text has been established by this Authority to read as follows:  
**PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES**
5. With regard to the abstract,
  - ☒ the text is approved as submitted by the applicant.
  - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
  - Figure No.            ☐ as suggested by the applicant. ☐ None of the figures.
  - ☐ because the applicant failed to suggest a figure.
  - ☐ because this figure better characterizes the invention.

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International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 33/24</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 96/30029</b> <b>(43) International Publication Date:</b> 3 October 1996 (03.10.96)
<b>(21) International Application Number:</b> PCT/GB96/00575 <b>(22) International Filing Date:</b> 19 March 1996 (19.03.96) <b>(30) Priority Data:</b> 9506126.3 25 March 1995 (25.03.95) GB <b>(71) Applicant (for all designated States except US):</b> JOHNSON MATTHEY PUBLIC LIMITED COMPANY [GB/GB]; 78 Hatton Garden, London EC1N 8JP (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> MURRER, Barry, Anthony [GB/GB]; 17 Camarvon Road, Reading, Berkshire RG1 5SB (GB). POWELL, Nigel, Anthony [GB/GB]; 4 Ibstock Close, Reading, Berkshire RG3 2NU (GB). <b>(74) Agents:</b> BREWER, Leonard, Stuart et al.; Johnson Matthey plc, Technology Centre, Blounts Court, Sonning Common, Reading RG4 9NH (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES  <b>(57) Abstract</b>  Selected lanthanum carbonate hydrates may be administered into the gastrointestinal tract, to treat hyperphosphataemia in patients with renal failure.		

**FOR THE PURPOSES OF INFORMATION ONLY**

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GA	Gabon			VN	Viet Nam

**PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES**

5           This invention concerns a novel and inventive pharmaceutical composition and method, more particularly it concerns a composition for the treatment of hyperphosphataemia.

10           Hyperphosphataemia is a particular problem of patients with renal failure, using dialysis equipment. Conventional dialysis fails to reduce levels of phosphate in the blood, so that the levels rise in time. It is known to control phosphate levels by the oral administration of aluminium salts, or calcium salts. With the known toxic effects of aluminium, aluminium-based therapy tends to be avoided. In the case

of calcium salts, calcium is absorbed rather readily from the gut, and in turn causes hypercalcaemia.

It has been suggested (Nakagawa *et al*, Trans Am Soc Intern Organs, 31,  
5 (1985) 155-9) that hydrous cerium oxide could be used as a bead in an ion-exchange  
column, to bind phosphate during dialysis. Japanese published patent application 61  
004 529 appears to cover the same idea, suggesting that the hydrous oxides of La, Ce  
and Y may be used in the column. However, although the rare earths are generally  
considered of low toxicity according to the Hodge-Sterner classification system (Am  
10 Ind Hyg Assoc Quart, 10, (1943), 93), their toxicity when given *iv*, which corresponds  
to use in a blood dialysis system, is significant and we are not aware that the suggested  
ion exchange system or any development thereof has met with widespread acceptance  
or has been tested clinically for hyperphosphataemia.

15 It appears that cerium oxide or oxalate was administered many years ago  
for different medical indications, but that this has fallen into complete disuse.

Japanese published patent application number 62-145024 (Asahi  
Chemical Ind KK) discloses that rare earth carbonates, bicarbonates or organic acid  
20 compounds may be used as phosphate binding agents. One example of said published  
application relates to the use of lanthanum carbonate, although in the tests described,  
cerium organic acid salts and carbonate gave better phosphate ion extraction than  
lanthanum carbonate. Example 11 of said published application prepares

$\text{La}_2(\text{CO}_3)_3 \cdot \text{H}_2\text{O}$ , ie the monohydrate; all the other Examples are directed to rare earth carbonates other than lanthanum carbonate.

We have now discovered that certain forms of lanthanum carbonate  
5 exhibit improved performance in a variety of tests, over standard commercial lanthanum carbonate, which is believed to be the octahydrate form, and over  $\text{La}_2(\text{CO}_3)_3 \cdot \text{H}_2\text{O}$  or similar compounds.

According to one aspect therefore, the present invention is the use of  
10 lanthanum carbonate of formula  $\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O}$  where x has a value from 3 to 6, preferably from 3.5 to 5, more especially from 3.8 to 4.5, for the preparation of a medicament for the treatment of hyperphosphataemia by administration into the gastrointestinal tract.

15 The invention further provides a pharmaceutical composition comprising said lanthanum carbonate, in admixture or association with a pharmaceutically acceptable diluent or carrier, in a form for administration into the gastrointestinal tract for the treatment of hyperphosphataemia.

20 The invention may also be expressed as a method of treatment of hyperphosphataemia in a patient with renal failure, comprising the administration of an effective dose of said lanthanum carbonate into the gastrointestinal tract.

According to another aspect, the present invention is a process for the preparation of lanthanum carbonate which comprises the steps of:

- (i) reacting lanthanum oxide with an acid which gives a soluble salt of lanthanum;
- (ii) reacting a solution of the thus obtained lanthanum salt with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and
- (iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

According to yet another aspect, the present invention is lanthanum carbonate when obtained by the above-mentioned process.

According to a further aspect, the present invention is lanthanum carbonate of the formula  $\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O}$  where  $x$  has a value from 3 to 6.

Embodiments of the present invention are described below, by way of example only, with reference to the accompanying drawings in which:

Figure 1 illustrates the phosphate-binding capability of lanthanum carbonates having different degrees of water of crystallisation;

Figure 2 illustrates the drying curves for five batches of lanthanum carbonate prepared by the method indicated in Example 1;

Figure 3 illustrates the XRD analysis of lanthanum carbonate  $4\text{H}_2\text{O}$  prepared by the method indicated in Example 2; and

Figure 4 illustrates the XRD analysis of lanthanum carbonate  $8.8\text{H}_2\text{O}$  of Sample 1 above.

5

For the tests described hereinafter, samples of lanthanum carbonate were obtained as follows:

Sample 1. Commercial lanthanum carbonate obtained from a chemical company. This was characterised by elemental analysis (La, C, H), TGA, X-ray powder diffraction and ir spectroscopy, to have the formula  $\text{La}_2(\text{CO}_3)_3 \cdot 8.8\text{H}_2\text{O}$ .

Samples 2 - 4 were prepared by heating portions of Sample 1 at varying temperatures for varying lengths of time, either under vacuum or at atmospheric pressure to obtain materials of formula  $\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O}$  where  $0 < x < 8$ .

20

Sample	Initial wt (g)	Temp (°C)	Time (min)	Vacuum (Y/N)	Wt loss (g)	x
2	5.00	175	240	Y	1.09	1.3
3	20.0	80	180	N	2.6	4.4
4	5.01	100	720*	N	0.96	2.2

\* Dried to constant weight.

Sample 5 is a sample of lanthanum carbonate which when analysed indicated a formula of  $\text{La}_2(\text{CO}_3)_3 \cdot 4\text{H}_2\text{O}$ .

Sample 6 is a sample of lanthanum carbonate prepared according to Example 1 below and having the formula  $\text{La}_2(\text{CO}_3)_3 \cdot 3.8\text{H}_2\text{O}$ .

In order to show that certain lanthanum carbonate hydrates are significantly different in phosphate binding activity from both lanthanum carbonate octahydrate and from  $\text{La}_2(\text{CO}_3)_3 \cdot \text{H}_2\text{O}$ , samples were tested as follows:

10

i) a stock solution was prepared by dissolving 13.75g of anhydrous  $\text{Na}_2\text{HPO}_4$ , 8.5g of NaCl in 1 litre deionised water.

ii) 100ml of the stock solution was adjusted to pH3 by the addition of concentrated HCl.

15

iii) A 5ml sample was taken and filtered through a  $0.02\mu\text{m}$  filter to give a Time 0 sample. This was analysed for phosphate using a Sigma Diagnostics Colorimetric Phosphorus test kit.

iv) 5ml fresh stock solution was added to re-establish 100ml, and the pH was re-adjusted to approximately 3.

20

v)  $\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O}$  as a dry powder was added in an amount according to the molecular weight of the particular hydrate, to give a two-fold molar excess of lanthanum over phosphate and stirred at room temperature.

vi) Sampling was carried out at time intervals from 0.5 to 10 minutes, and the percentage of phosphate was determined as in iii) above. The results are shown in the Table 1 below.

5

TABLE 1

10

15

20

TIME (Minutes)	% PHOSPHATE REMOVED					
	Sample					
	1	2	3	4	5	6
0						
0.5		13.4	18.8	15.1	22.9	31.4
1	29	18.4	31.5	26.8	40.4	55.5
1.5		25.4	43.1	36	55.2	74.8
2		28.1	50.6	45.3	69.5	88.1
2.5		30.8	60.5	51.8	79.9	95.3
3		34.4	69	57.6	90.3	99.6
4						100
5	70.5	39.9	96.5	76.3	100	100
10	100	ND	99.1	ND	100	100

It can readily be seen from Table 1 that Sample 3 ( $\text{La}_2(\text{CO}_3)_3 \cdot 4.4\text{H}_2\text{O}$ ); Sample 5 ( $\text{La}_2(\text{CO}_3)_3 \cdot 4\text{H}_2\text{O}$ ) and Sample 6 ( $\text{La}_2(\text{CO}_3)_3 \cdot 3.8\text{H}_2\text{O}$ ) bind phosphate appreciably quicker than the  $8.8\text{H}_2\text{O}$ ,  $1.3\text{H}_2\text{O}$  or  $2.2\text{H}_2\text{O}$  forms. We believe that the results for  $\text{La}_2(\text{CO}_3)_3 \cdot 1.3\text{H}_2\text{O}$  are in agreement with the results shown in the above mentioned Japanese published patent application number 62-145024 where for  $\text{La}_2(\text{CO}_3)_3 \cdot \text{H}_2\text{O}$ , only 90% removal is shown after 120 minutes.

30

It can also be readily seen from Figure 1 of the accompanying drawings that the highest phosphate removal is obtained with lanthanum carbonates having 3 to 6 molecules of water.

5                   The present invention offers the possibility of binding phosphate without any incursion of lanthanum into the blood stream, where toxic effects can cause problems. The specified lanthanum carbonate has negligible absorption from the gut, as shown by the *in vivo* tests described below.

10                   Throughout this document, the term "treatment" is intended to include preventative treatment.

Processes for preparing lanthanum carbonates according to the present invention are described by way of illustration in the following Examples 1 and 2.

15

### **EXAMPLE 1**

Lanthanum oxide (1.5kg, 4.58mol) was suspended in water (5.5 litres) in a 20 litre flask. Nitric acid (Analar grade, 69%, SG 1.42, 1.88 litres, 29.23mol) was added to the stirred solution over 1.5 hours at such a rate as to keep the temperature between 60-80°C. The resulting lanthanum nitrate solution was left to cool to room temperature and filtered. A solution of sodium carbonate (1.65kg, 15.57mol) in water (7.75 litres) was added to the stirred lanthanum nitrate solution over 45 minutes. At the end of the addition the pH of the suspension was 9.74. The suspension was left

20

overnight, filtered (Buchner funnel, 540 paper) and dried on the filter in a current of air for 30 minutes. The solid was then re-suspended in water, stirred for 40 minutes and filtered. This procedure was repeated to give a total of six washes, when the nitrate concentration in the filtrate was <500ppm. The final material (4.604kg) was divided between three Pyrex dishes and a sample from each analysed for water content. (By decomposition of weighed sample of  $(\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O})$  at  $1050^\circ\text{C}$ , 2 hours to  $\text{La}_2\text{O}_3$ ). The dishes were then placed in a fan oven at  $80^\circ\text{C}$  and the weight loss of each dish monitored until the material of the required degree hydration was obtained. The progress of the drying is shown below

Time (hours)	mol $\text{H}_2\text{O}/\text{La}$		
	Dish 1	Dish 2	Dish 3
3.50	10.9	13.5	12.6
12	5.7	6.0	5.2
14	5.3	5.4	4.6
16	4.9	5.1	4.3
17	4.4	4.6	3.8
19.5	3.8	4.0	3.2

Drying curves for five batches produced by this route are shown in

Figure 2.

$\text{La}_2(\text{CO}_3)_3 \cdot 3.8\text{H}_2\text{O}$  from dish 1 was selected as Sample 6 for the phosphate binding tests set forth in Table 1.

**EXAMPLE 2**

The process of Example 1 was repeated but using hydrochloric acid (12.28M, 2.48 litres) in place of nitric acid to dissolve lanthanum oxide (1.5kg). The yield of crude product after six washes was 4.378kg. The product was divided in three approximately equal portions in Pyrex dishes and dried in a fan oven at 80°C. After 2 hours a sample was taken from each tray and water analysed by decomposition to lanthanum oxide as described above. These figures were used to calculate the weight loss needed to give material of the required composition. The time course of the drying process is shown below.

15

20

Time (hours)	mol H <sub>2</sub> O/La		
	Dish 1	Dish 2	Dish 3
2	21.3	22.1	20.4
5.5	12.3	13.2	12.2
9	7.9	8.0	7.6
11.5	6.9	7.0	6.6
17	4.9	5.1	4.6
18.5	4.6	4.8	4.2
19.5	4.4	4.6	4.1
20	4.3	4.6	4.0

Samples were taken from each dish, combined and analysed. The following results were obtained:

25

	Found	Calculation for $\text{La}_2(\text{CO}_3)_3 \cdot 4\text{H}_2\text{O}$
% La (gravimetric)	52.38%	52.4%
carbonate (titration)	5.76mol/g	5.66mol/g
$\text{H}_2\text{O}$ (NMR)	13.06%	13.59%

5

The XRD analysis for lanthanum carbonate  $4\text{H}_2\text{O}$  prepared by the method of Example 2 is illustrated in Figure 3.

10

Figure 4 illustrates the XRD of lanthanum carbonate  $8.8\text{H}_2\text{O}$  and it is evident that it has a different crystalline structure from lanthanum carbonate  $4\text{H}_2\text{O}$  prepared by the method of Example 2. The XRD analysis of lanthanum carbonate  $4\text{H}_2\text{O}$  prepared by the method of Example 1 was similar to the XRD analysis of lanthanum carbonate  $4\text{H}_2\text{O}$  prepared by the method of Example 2.

15

Pharmaceutical compositions for oral administration according to the invention may be formulated and manufactured using methods well known in the art. Suitable diluents or carriers are also well known. The compositions may desirably be in a dosage form, to provide a single daily dose, or a number of sub-daily dosages. Conventional pharmacological methods may be used to ascertain suitable dose levels.

20

The level of phosphate in the food that an individual ingests is important. Daily dosages are indicated to be in the range 0.1 to 50g, preferably about 0.5 to 15g. Suitable forms for oral administration include solid forms such as tablets, capsules and dragees and liquid forms such as suspensions or syrups. In addition to diluents and carriers, it is conventional in the formulation of oral preparations to include non-active

ingredients such as thickeners, taste-improving components and colouring agents. The said carbonate may also be coated or treated to provide delayed-release forms. Preferably, the required daily dosage is given in tablet form, *eg* chewable tablet form, to be taken with meals. A suitable daily dosage of about 2g for 70kg man, should be compared with a daily dosage of 20g for a commercial calcium-based phosphate binding composition.

To demonstrate that the lanthanum carbonate of the invention (or lanthanum phosphate formed after binding to phosphate in the gut) is fully excreted and does not pass out of the gut into the circulation system when given orally, three rats were dosed with 20mg/kg of  $\text{La}_2(\text{CO}_3)_3 \cdot 4\text{H}_2\text{O}$  (Sample 5) and kept in metabolic cages where faeces and urine could be collected. The results are shown in Table 2 below.

Animal No.	Time (hours)	% La Recovered
1	24	103.2
1	48	0.1
1	72	<0.2
1	Total	103.3
2	24	75.3
2	48	23
2	72	1.2
2	Total	99.5

Animal No	Time (hours)	%La Recovered
3	24	93.8
3	48	10
3	72	0.1
3	Total	103.8

5

It can be seen that after 72 hours, all of the lanthanum has been excreted. In the urine samples, the amount of lanthanum was below detection limits.

10

After the test, the rats were sacrificed, and kidney, liver and femur were analysed for lanthanum. In all cases, the amount of lanthanum was below 0.1ppm.

**CLAIMS**

1. A pharmaceutical composition for the treatment of hyperphosphataemia, comprising lanthanum carbonate of formula



where x has a value from 3 to 6, in admixture or association with a pharmaceutically acceptable diluent or carrier.

2. A composition according to claim 1, wherein in the lanthanum carbonate, x has a value from 3.5 to 5.

10

3. A composition according to claim 2, wherein in the lanthanum carbonate, x has a value from 3.8 to 4.5.

4. A composition according to any one of claims 1 to 3, in a form suitable for oral administration.

15

5. A composition according to any one of claims 1 to 4 in unit dosage form to provide from 0.1 to 20g/day.

20

6. The use of lanthanum carbonate as defined in any one of claims 1 to 3, for the preparation of a medicament for the treatment of hyperphosphataemia by administration into the gastrointestinal tract.

7. A process for the preparation of lanthanum carbonate as defined in any one of claims 1 to 3 which comprises the steps of:

(i) reacting lanthanum oxide with an acid which gives a soluble salt of lanthanum;

(ii) reacting a solution of the thus obtained lanthanum salt with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and

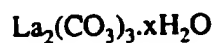
(iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

8. A process as claimed in claim 7 wherein the acid is nitric acid or hydrochloric acid.

9. A process as claimed in claim 7 or 8 wherein the alkali metal carbonate is sodium carbonate.

10. Lanthanum carbonate prepared according to the process of any of claims 7, 8 or 9.

11. Lanthanum carbonate of the formula



where x has a value from 3 to 6.

Fig. 1

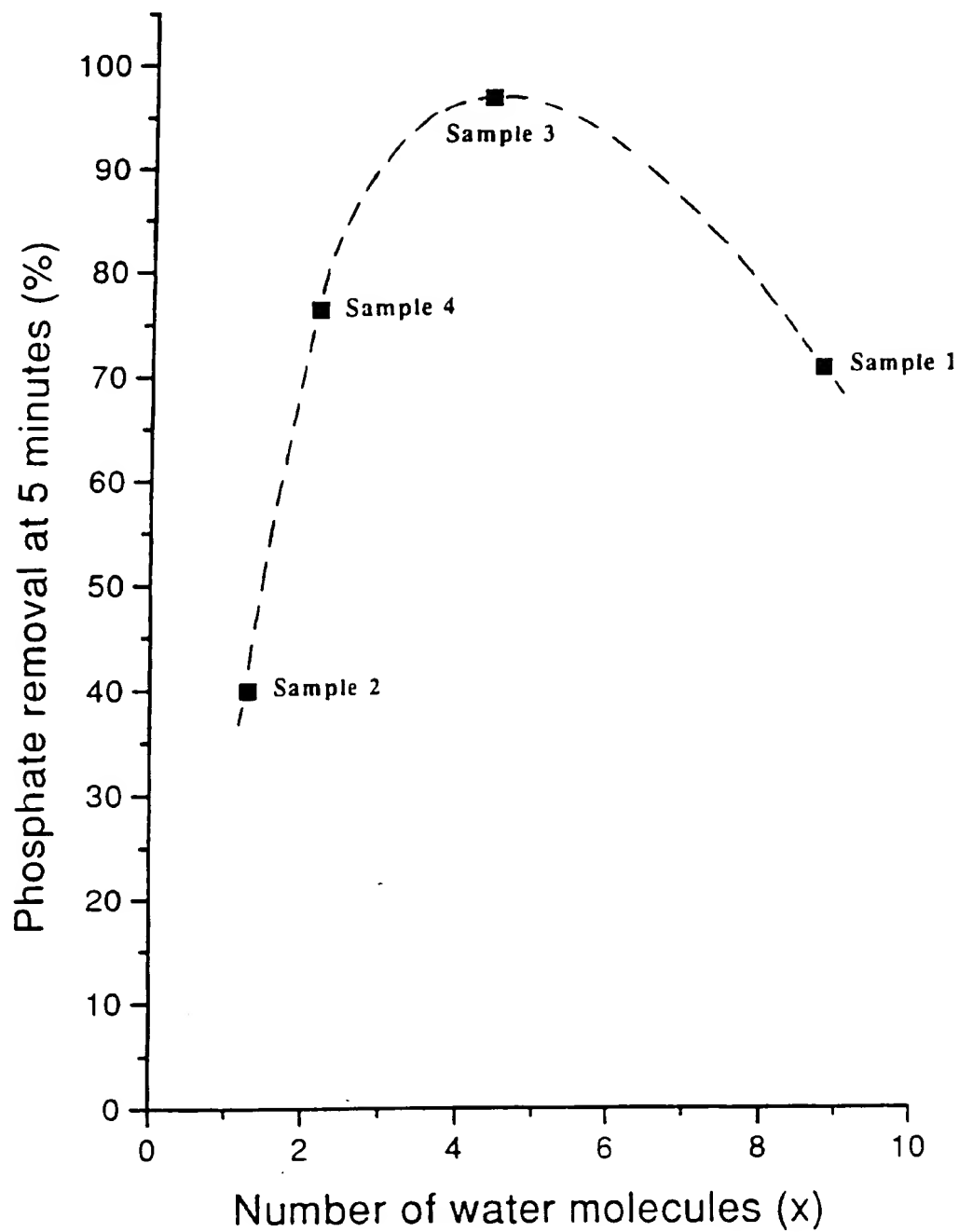


Fig. 2

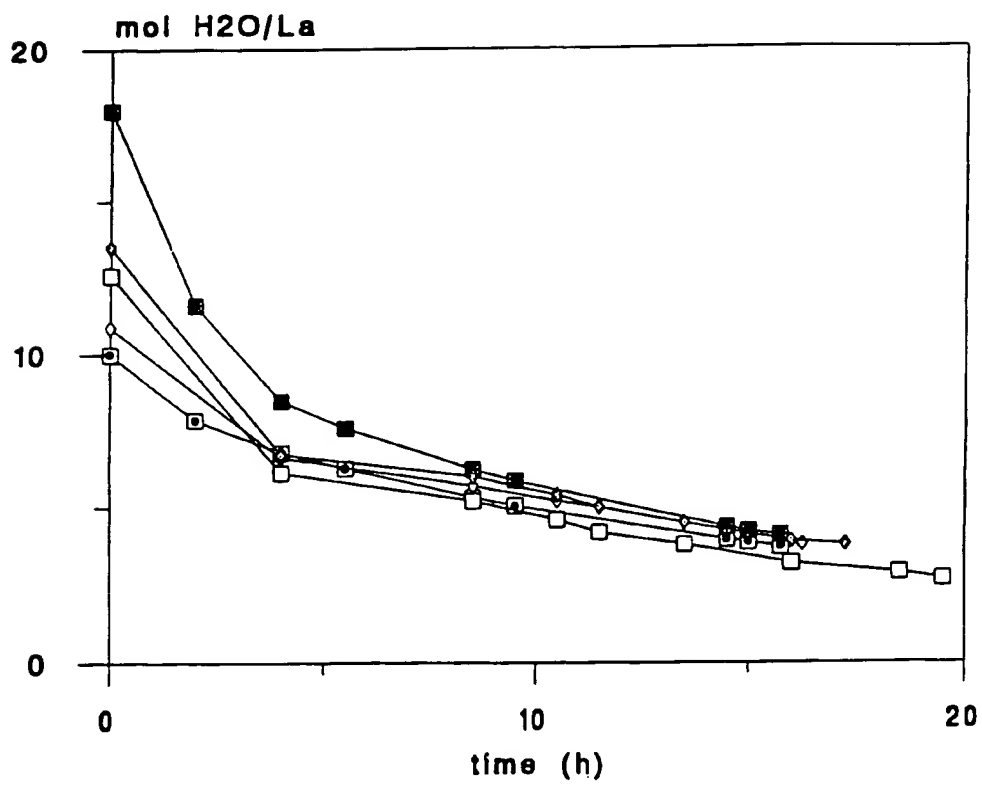


Fig. 3

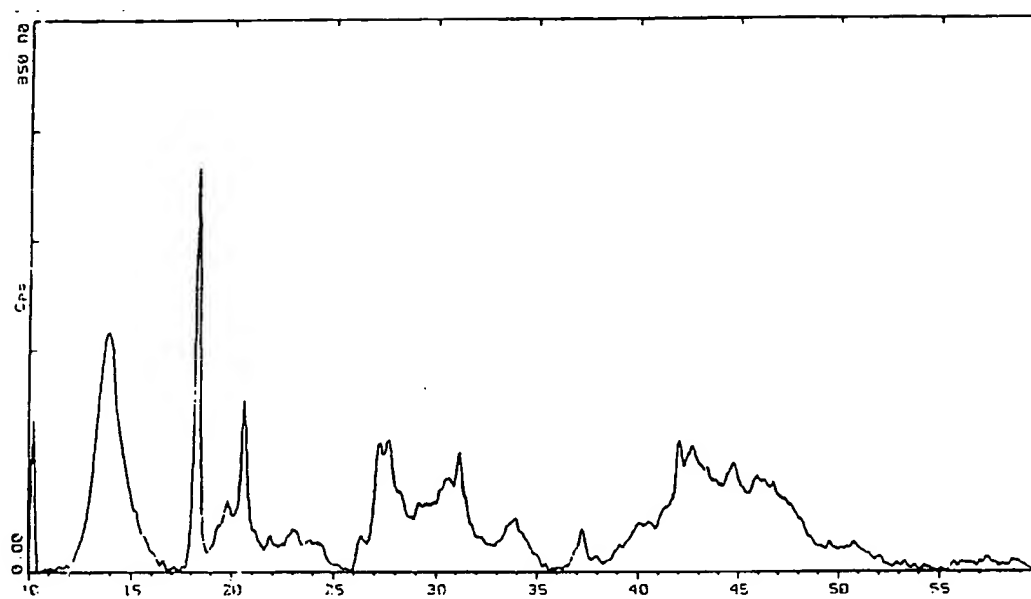
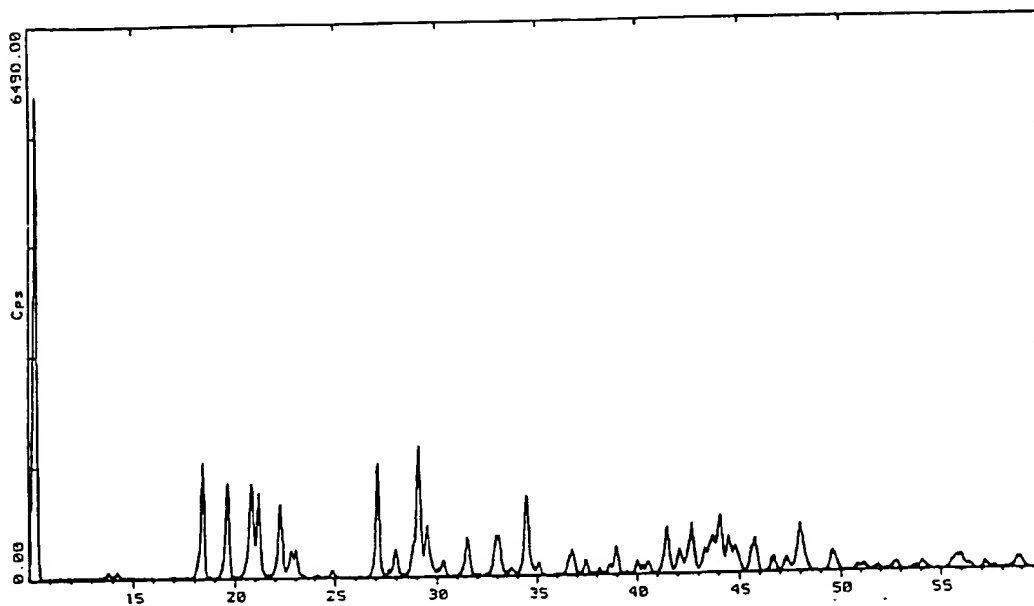


Fig.4



**MBUS 1126A**

**PHARMACEUTICAL COMPOSITION AND METHOD**

5 This invention concerns a novel and inventive pharmaceutical composition and method, more particularly it concerns a composition for the treatment of hyperphosphataemia.

10 Hyperphosphataemia is a particular problem of patients with renal failure, using dialysis equipment. Conventional dialysis fails to reduce levels of phosphate in the blood, so that the levels rise in time. It is known to control phosphate levels by the oral administration of aluminium salts, or calcium salts. With the known toxic effects of aluminium, aluminium-based therapy tends to be avoided. In the case of calcium salts, calcium is absorbed rather readily from the gut, and in turn causes hypercalcaemia.

It has been suggested (Nakagawa *et al*, Trans Am Soc Intern Orga., 31, (1985) 155-9) that hydrous cerium oxide could be used as a bead in an ion-exchange column, to bind phosphate during dialysis. Japanese published patent application 61 004 529 appears to cover the same idea, suggesting that the hydrous oxides of La, Ce and Y may be used in the column. However, although the rare earths are generally considered of low toxicity according to the Hodge-Sterner classification system (Am Ind Hyg Assoc Quart, 10, (1943), 93), their toxicity when given *iv*, which corresponds to use in a blood dialysis system, is significant and we are not aware that the suggested ion exchange system or any development thereof has met with widespread acceptance or has been tested clinically for hyperphosphataemia.

It appears that cerium oxide or oxalate had been administered many years ago for different medical indications, but that this has fallen into complete disuse.

Japanese published patent application number 62-145024 (Asahi Chemical Ind KK) discloses that rare earth carbonates, bicarbonates or organic acid compounds may be used as phosphate binding agents. One example relates to the use of lanthanum carbonate, although in the tests described, cerium organic acid salts and carbonate gave better phosphate ion extraction than lanthanum carbonate. (It is our view that the tests described are not representative of conditions in the gastrointestinal tract, since measurements are taken at pH7.) Example 11 of said

published application prepares  $\text{La}_2(\text{CO}_3)_3 \cdot \text{H}_2\text{O}$ , that is a monohydrate; all other Examples are quite specific as to the amount of water of crystallisation.

5 We have now discovered that certain forms of lanthanum carbonate exhibit improved performance in a variety of tests, over standard commercial lanthanum carbonate, which is believed to be the octahydrate form, and over  $\text{La}_2(\text{CO}_3)_3 \cdot \text{H}_2\text{O}$  or similar compounds.

10 A form which analyses as the tetrahydrate form may be prepared by heating the octahydrate for sufficient time to drive off 4 molecules of water of crystallisation per mol of lanthanum carbonate, *eg* 60 to 80°C for 2 hours. An amorphous solid is obtained. Other routes for preparation of the tetrahydrate form may be used, or there may be commercial sources, although commercial sources do not usually analyse for water of crystallisation.

15

For the tests described hereinafter, samples of lanthanum carbonate were obtained as follows:

20 **Sample 1.** Commercial lanthanum carbonate obtained from a chemical company. This was characterised by elemental analysis (La, C, H), TGA, X-ray powder diffraction and ir spectroscopy, to have the formula  $\text{La}_2(\text{CO}_3)_3 \cdot 8.8\text{H}_2\text{O}$ .

Samples 2 - 4 were prepared by heating portions of Sample 1 at varying temperatures for varying lengths of time, either under vacuum or at atmospheric pressure to obtain materials of formula  $\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O}$  where  $0 < x < 8$ .

5

Sample	Initial wt (g)	Temp (°C)	Time (min)	Vacuum (Y/N)	Wt loss (g)	x
2	5.00	175	240	Y	1.09	1.3
3	20.0	80	180	N	2.6	4.4
4	5.01	100	720*	N	0.96	2.2

10

\* Dried to constant weight.

A sample of  $\text{La}_2(\text{CO}_3)_3 \cdot 4\text{H}_2\text{O}$  was obtained and allocated Sample number 5.

15

In order to show that lanthanum carbonate tetrahydrate is significantly different in phosphate binding activity from both conventional, commercial lanthanum carbonate octahydrate and from  $\text{La}_2(\text{CO}_3)_3 \cdot \text{H}_2\text{O}$ , samples were tested as follows:

20

- i) a stock solution was prepared by dissolving 13.75g of anhydrous  $\text{Na}_2\text{HPO}_4$ , 8.5g of NaCl in 1 litre 18MΩ water.
- ii) 100ml of the stock solution was adjusted to pH3 by the addition of concentrated HCl.

iii) A 5ml sample was taken and filtered through a 0.02 $\mu$ m filter to give a Time 0 sample. This was analysed for phosphate using a Sigma Diagnostics Colorimetric Phosphorus test kit.

iv) 5ml fresh stock solution was added to re-establish 100ml, and the pH was re-adjusted to approximately 3.

v)  $\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O}$  as a dry powder was added in an amount according to the molecular weight of the particular hydrate, to give a two-fold molar excess of lanthanum over phosphate and stirred at room temperature.

vi) Sampling was carried out at time intervals from 0.5 to 10 minutes, and the percentage of phosphate was determined as in iii) above. The results are shown in the Table 1 below.

TABLE 1

TIME (Minutes)	% PHOSPHATE REMOVED				
	Sample				
	1	2	3	4	5
0					
0.5		13.4	18.8	15.1	22.9
1	29.0	18.4	31.5	26.8	40.4
1.5		25.4	43.1	36.0	55.2
2		28.1	50.6	45.3	69.5
2.5		30.8	60.5	51.8	79.9
3		34.4	69.0	57.6	90.3
5	70.5	39.9	96.5	76.3	100
10	100	ND	99.1	ND	100

It can readily be seen that Samples 3 and 5 ( $\text{La}_2(\text{CO}_3)_3 \cdot 4\text{H}_2\text{O}$  and  $\text{La}_2(\text{CO}_3)_3 \cdot 4.4\text{H}_2\text{O}$ ) bind phosphate appreciably quicker than the  $.8\text{H}_2\text{O}$  or  $.1.3\text{H}_2\text{O}$  forms. We believe that these results are in agreement with the results shown in the said Japanese patent application where for  $\text{La}_2(\text{CO}_3)_3 \cdot \text{H}_2\text{O}$ , only 90% removal is shown after 120 mins.

We also believe that testing at pH3 is more representative of conditions in the upper gastrointestinal tract than pH7, and also that it is important to remove phosphate as early as possible in the digestion process.

The present invention offers the possibility of binding phosphate without any incursion of lanthanum into the blood stream, where toxic effects including, we believe, calcium antagonism, can cause problems. The specific lanthanum carbonate has negligible absorption from the gut, as shown by the *in vivo* tests described below.

Throughout this document, the term "treatment" is intended to include preventative treatment.

The present invention, therefore, is defined as the use of lanthanum carbonate of formula  $\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O}$  where x has a value from 3 to 6, preferably from 3.5 to 5, more especially from 3.9 to 4.5, for the preparation of a medicament for the treatment of hyperphosphataemia by administration into the gastrointestinal tract.

The invention further provides a pharmaceutical composition comprising said lanthanum carbonate, in admixture or association with a pharmaceutically acceptable diluent or carrier, in a form for administration into the gastrointestinal tract for the treatment of hyperphosphataemia.

5

The invention may also be expressed as a method of treatment of hyperphosphataemia in a patient with renal failure, comprising the administration of an effective dose of said lanthanum carbonate into the gastrointestinal tract.

10

Pharmaceutical compositions for oral administration according to the invention may be formulated and manufactured using methods well known in the art. Suitable diluents or carriers are also well known. The compositions may desirably be in a dosage form, to provide a single daily dose, or a number of sub-daily dosages. Conventional pharmacological methods may be used to ascertain suitable dose levels. The level of phosphate in the food that an individual ingests is important. Daily dosages are indicated to be in the range 1 to 50g, preferably about 1.5 to 15g. Suitable forms for oral administration include solid forms such as tablets, capsules and dragees and liquid forms such as suspensions or syrups. In addition to diluents and carriers, it is conventional in the formulation of oral preparations to include non-active ingredients such as thickeners, taste-improving components and colouring agents. The said carbonate may also be coated or treated to provide delayed-release forms. Preferably, the required daily dosage is given in tablet form, *eg* chewable tablet form, to be taken with meals. A suitable daily

15

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dosage of about 2g for 70kg man, should be compared with a daily dosage of 2g for a commercial calcium-based phosphate binding composition.

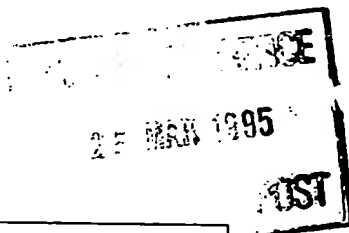
To demonstrate that the lanthanum carbonate of the invention (or lanthanum phosphate) is fully excreted and does not pass out of the gut into the system when given orally, three rats were dosed with 20mg/kg of  $\text{La}_2(\text{CO}_3)_3 \cdot 4\text{H}_2\text{O}$  and kept in metabolic cages where faeces and urine could be collected. The results are shown in Table 2 below.

Animal No.	Time (hours)	% La Recovered
1	24	103.2
1	48	0.1
1	72	<0.2
1	Total	103.3
2	24	75.3
2	48	23.0
2	72	1.2
2	Total	99.5
3	24	93.8
3	48	10.0
3	72	0.1
3	Total	103.8

It can be seen that after 72 hours, all of the lanthanum has been excreted. In the urine samples, the amount of lanthanum was below detection limits.

For official use

25 MAR 1995



26MAR95 E118662-1 001091  
P01/7700 25.00

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#### Notes

Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071-438 4700).

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

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After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977 and will inform the applicant if such prohibition or restriction is necessary. Applicants resident in the United Kingdom are also reminded that under Section 23, applications may not be filed abroad without written permission unless an application has been filed not less than 6 weeks previously in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction revoked.

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## Request for grant of a Patent Form 1/77

Patents Act 1977

### 1 Title of invention

1 Please give the title  
of the invention

PHARMACEUTICAL COMPOSITION AND METHOD

### 2 Applicant's details

☒ First or only applicant

2a If you are applying as a corporate body please give:

Corporate name

JOHNSON MATTHEY PUBLIC LIMITED COMPANY

Country (and State  
of incorporation, if  
appropriate) GB

2b If you are applying as an individual or one of a partnership please give in full:

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Forenames

2c In all cases, please give the following details:

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Country GB

ADP number  
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S36268005

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3991437001

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- ⑦ The answer must be 'No' if:
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  - there is an inventor who is not an applicant, **or**
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- ⑨ You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

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A completed fee sheet should preferably accompany the fee.

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7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

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➡ **A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).**

## ⑧ Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77

NIL

Claim(s)

1

Description

9

Abstract

1

Drawing(s)

8b Which of the following documents also accompanies the application?

Priority documents (please state how many)

Translation(s) of Priority documents (please state how many)

Patents Form 7/77 – Statement of Inventorship and Right to Grant  
(please state how many)

Patents Form 9/77 – Preliminary Examination/Search

YES

Patents Form 10/77 – Request for Substantive Examination

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MBUS 1126A

**5 Claiming an earlier application date**

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

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**6 Declaration of priority**

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number (if known)	Filing date (day, month, year)
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6 If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

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After the test, the rats were sacrificed, and kidney, liver and femur were analysed for lanthanum. In all cases, the amount of lanthanum was below 0.1ppm.

**CLAIMS**

1. A pharmaceutical composition for the treatment of hyperphosphataemia, comprising lanthanum carbonate of formula



where x has a value from 3 to 6, in admixture or association with a pharmaceutically acceptable diluent or carrier.

10 2. A composition according to claim 1, wherein in the lanthanum carbonate, x has a value from 3.5 to 5.

3. A composition according to claim 2, wherein in the lanthanum carbonate, x has a value from 3.9 to 4.5.

15 4. A composition according to any one of claims 1 to 3, in a form suitable for oral administration.

5. A composition according to any one of claims 1 to 4 in unit dosage form to provide from 1 to 20g/day.

20

6. The use of lanthanum carbonate as defined in any one of claims 1 to 3, for the preparation of a medicament for the treatment of hyperphosphataemia by administration into the gastrointestinal tract.

PCT

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/GB96/00575 <b>(22) International Filing Date:</b> 19 March 1996 (19.03.96) <b>(30) Priority Data:</b> 9506126.3                      25 March 1995 (25.03.95)                      GB <b>(71) Applicant (for all designated States except US):</b> JOHNSON MATTHEY PUBLIC LIMITED COMPANY [GB/GB]; 78 Hatton Garden, London EC1N 8JP (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> MURRER, Barry, Anthony [GB/GB]; 17 Camarvon Road, Reading, Berkshire RG1 5SB (GB). POWELL, Nigel, Anthony [GB/GB]; 4 Ibstock Close, Reading, Berkshire RG3 2NU (GB). <b>(74) Agents:</b> BREWER, Leonard, Stuart et al.; Johnson Matthey plc, Technology Centre, Blounts Court, Sonning Common, Reading RG4 9NH (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES <b>(57) Abstract</b> <p>Selected lanthanum carbonate hydrates may be administered into the gastrointestinal tract, to treat hyperphosphataemia in patients with renal failure.</p>		

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## PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES

This invention concerns a novel and inventive pharmaceutical composition and method, more particularly it concerns a composition for the treatment  
5 of hyperphosphataemia.

Hyperphosphataemia is a particular problem of patients with renal failure, using dialysis equipment. Conventional dialysis fails to reduce levels of phosphate in the blood, so that the levels rise in time. It is known to control phosphate  
10 levels by the oral administration of aluminium salts, or calcium salts. With the known toxic effects of aluminium, aluminium-based therapy tends to be avoided. In the case

of calcium salts, calcium is absorbed rather readily from the gut, and in turn causes hypercalcaemia.

It has been suggested (Nakagawa *et al*, Trans Am Soc Intern Organs, 31, (1985) 155-9) that hydrous cerium oxide could be used as a bead in an ion-exchange column, to bind phosphate during dialysis. Japanese published patent application 61 004 529 appears to cover the same idea, suggesting that the hydrous oxides of La, Ce and Y may be used in the column. However, although the rare earths are generally considered of low toxicity according to the Hodge-Sterner classification system (Am Ind Hyg Assoc Quart, 10, (1943), 93), their toxicity when given *iv*, which corresponds to use in a blood dialysis system, is significant and we are not aware that the suggested ion exchange system or any development thereof has met with widespread acceptance or has been tested clinically for hyperphosphataemia.

It appears that cerium oxide or oxalate was administered many years ago for different medical indications, but that this has fallen into complete disuse.

Japanese published patent application number 62-145024 (Asahi Chemical Ind KK) discloses that rare earth carbonates, bicarbonates or organic acid compounds may be used as phosphate binding agents. One example of said published application relates to the use of lanthanum carbonate, although in the tests described, cerium organic acid salts and carbonate gave better phosphate ion extraction than lanthanum carbonate. Example 11 of said published application prepares

$\text{La}_2(\text{CO}_3)_3 \cdot \text{H}_2\text{O}$ , *ie* the monohydrate; all the other Examples are directed to rare earth carbonates other than lanthanum carbonate.

We have now discovered that certain forms of lanthanum carbonate  
5 exhibit improved performance in a variety of tests, over standard commercial lanthanum carbonate, which is believed to be the octahydrate form, and over  $\text{La}_2(\text{CO}_3)_3 \cdot \text{H}_2\text{O}$  or similar compounds.

According to one aspect therefore, the present invention is the use of  
10 lanthanum carbonate of formula  $\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O}$  where  $x$  has a value from 3 to 6, preferably from 3.5 to 5, more especially from 3.8 to 4.5, for the preparation of a medicament for the treatment of hyperphosphataemia by administration into the gastrointestinal tract.

15 The invention further provides a pharmaceutical composition comprising said lanthanum carbonate, in admixture or association with a pharmaceutically acceptable diluent or carrier, in a form for administration into the gastrointestinal tract for the treatment of hyperphosphataemia.

20 The invention may also be expressed as a method of treatment of hyperphosphataemia in a patient with renal failure, comprising the administration of an effective dose of said lanthanum carbonate into the gastrointestinal tract.

According to another aspect, the present invention is a process for the preparation of lanthanum carbonate which comprises the steps of:

- 5 (i) reacting lanthanum oxide with an acid which gives a soluble salt of lanthanum;
- (ii) reacting a solution of the thus obtained lanthanum salt with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and
- (iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

10 According to yet another aspect, the present invention is lanthanum carbonate when obtained by the above-mentioned process.

According to a further aspect, the present invention is lanthanum  
15 carbonate of the formula  $\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O}$  where x has a value from 3 to 6.

Embodiments of the present invention are described below, by way of example only, with reference to the accompanying drawings in which:

20 Figure 1 illustrates the phosphate-binding capability of lanthanum carbonates having different degrees of water of crystallisation;

Figure 2 illustrates the drying curves for five batches of lanthanum carbonate prepared by the method indicated in Example 1;

Figure 3 illustrates the XRD analysis of lanthanum carbonate  $4\text{H}_2\text{O}$  prepared by the method indicated in Example 2; and

Figure 4 illustrates the XRD analysis of lanthanum carbonate  $8.8\text{H}_2\text{O}$  of Sample 1 above.

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For the tests described hereinafter, samples of lanthanum carbonate were obtained as follows:

**Sample 1.** Commercial lanthanum carbonate obtained from a chemical company.

10

This was characterised by elemental analysis (La, C, H), TGA, X-ray powder diffraction and ir spectroscopy, to have the formula  $\text{La}_2(\text{CO}_3)_3 \cdot 8.8\text{H}_2\text{O}$ .

**Samples 2 - 4** were prepared by heating portions of Sample 1 at varying temperatures for varying lengths of time, either under vacuum or at atmospheric pressure to obtain materials of formula  $\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O}$  where  $0 < x < 8$ .

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Sample	Initial wt (g)	Temp (°C)	Time (min)	Vacuum (Y/N)	Wt loss (g)	x
2	5.00	175	240	Y	1.09	1.3
3	20.0	80	180	N	2.6	4.4
4	5.01	100	720*	N	0.96	2.2

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\* Dried to constant weight.

Sample 5 is a sample of lanthanum carbonate which when analysed indicated a formula of  $\text{La}_2(\text{CO}_3)_3 \cdot 4\text{H}_2\text{O}$ .

Sample 6 is a sample of lanthanum carbonate prepared according to Example 1 below and having the formula  $\text{La}_2(\text{CO}_3)_3 \cdot 3.8\text{H}_2\text{O}$ .

In order to show that certain lanthanum carbonate hydrates are significantly different in phosphate binding activity from both lanthanum carbonate octahydrate and from  $\text{La}_2(\text{CO}_3)_3 \cdot \text{H}_2\text{O}$ , samples were tested as follows:

i) a stock solution was prepared by dissolving 13.75g of anhydrous  $\text{Na}_2\text{HPO}_4$ , 8.5g of NaCl in 1 litre deionised water.

ii) 100ml of the stock solution was adjusted to pH3 by the addition of concentrated HCl.

iii) A 5ml sample was taken and filtered through a  $0.02\mu\text{m}$  filter to give a Time 0 sample. This was analysed for phosphate using a Sigma Diagnostics Colorimetric Phosphorus test kit.

iv) 5ml fresh stock solution was added to re-establish 100ml, and the pH was re-adjusted to approximately 3.

v)  $\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O}$  as a dry powder was added in an amount according to the molecular weight of the particular hydrate, to give a two-fold molar excess of lanthanum over phosphate and stirred at room temperature.

vi) Sampling was carried out at time intervals from 0.5 to 10 minutes, and the percentage of phosphate was determined as in iii) above. The results are shown in the Table 1 below.

TABLE 1

TIME (Minutes)	% PHOSPHATE REMOVED					
	Sample					
	1	2	3	4	5	6
0						
0.5		13.4	18.8	15.1	22.9	31.4
1	29	18.4	31.5	26.8	40.4	55.5
1.5		25.4	43.1	36	55.2	74.8
2		28.1	50.6	45.3	69.5	88.1
2.5		30.8	60.5	51.8	79.9	95.3
3		34.4	69	57.6	90.3	99.6
4						100
5	70.5	39.9	96.5	76.3	100	100
10	100	ND	99.1	ND	100	100

It can readily be seen from Table 1 that Sample 3 ( $\text{La}_2(\text{CO}_3)_3 \cdot 4.4\text{H}_2\text{O}$ ); Sample 5 ( $\text{La}_2(\text{CO}_3)_3 \cdot 4\text{H}_2\text{O}$ ) and Sample 6 ( $\text{La}_2(\text{CO}_3)_3 \cdot 3.8\text{H}_2\text{O}$ ) bind phosphate appreciably quicker than the  $8.8\text{H}_2\text{O}$ ,  $1.3\text{H}_2\text{O}$  or  $2.2\text{H}_2\text{O}$  forms. We believe that the results for  $\text{La}_2(\text{CO}_3)_3 \cdot 1.3\text{H}_2\text{O}$  are in agreement with the results shown in the above mentioned Japanese published patent application number 62-145024 where for  $\text{La}_2(\text{CO}_3)_3 \cdot \text{H}_2\text{O}$ , only 90% removal is shown after 120 minutes.

It can also be readily seen from Figure 1 of the accompanying drawings that the highest phosphate removal is obtained with lanthanum carbonates having 3 to 6 molecules of water.

5                   The present invention offers the possibility of binding phosphate without any incursion of lanthanum into the blood stream, where toxic effects can cause problems. The specified lanthanum carbonate has negligible absorption from the gut, as shown by the *in vivo* tests described below.

10                   Throughout this document, the term "treatment" is intended to include preventative treatment.

Processes for preparing lanthanum carbonates according to the present invention are described by way of illustration in the following Examples 1 and 2.

15

### **EXAMPLE 1**

20                   Lanthanum oxide (1.5kg, 4.58mol) was suspended in water (5.5 litres) in a 20 litre flask. Nitric acid (Analar grade, 69%, SG 1.42, 1.88 litres, 29.23mol) was added to the stirred solution over 1.5 hours at such a rate as to keep the temperature between 60-80°C. The resulting lanthanum nitrate solution was left to cool to room temperature and filtered. A solution of sodium carbonate (1.65kg, 15.57mol) in water (7.75 litres) was added to the stirred lanthanum nitrate solution over 45 minutes. At the end of the addition the pH of the suspension was 9.74. The suspension was left

overnight, filtered (Buchner funnel, 540 paper) and dried on the filter in a current of air for 30 minutes. The solid was then re-suspended in water, stirred for 40 minutes and filtered. This procedure was repeated to give a total of six washes, when the nitrate concentration in the filtrate was <500ppm. The final material (4.604kg) was divided between three Pyrex dishes and a sample from each analysed for water content. (By decomposition of weighed sample of  $(\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O})$  at  $1050^\circ\text{C}$ , 2 hours to  $\text{La}_2\text{O}_3$ ). The dishes were then placed in a fan oven at  $80^\circ\text{C}$  and the weight loss of each dish monitored until the material of the required degree hydration was obtained. The progress of the drying is shown below

Time (hours)	mol $\text{H}_2\text{O}/\text{La}$		
	Dish 1	Dish 2	Dish 3
3.50	10.9	13.5	12.6
12	5.7	6.0	5.2
14	5.3	5.4	4.6
16	4.9	5.1	4.3
17	4.4	4.6	3.8
19.5	3.8	4.0	3.2

Drying curves for five batches produced by this route are shown in Figure 2.

$\text{La}_2(\text{CO}_3)_3 \cdot 3.8\text{H}_2\text{O}$  from dish 1 was selected as Sample 6 for the phosphate binding tests set forth in Table 1.

**EXAMPLE 2**

The process of Example 1 was repeated but using hydrochloric acid (12.28M, 2.48 litres) in place of nitric acid to dissolve lanthanum oxide (1.5kg). The yield of crude product after six washes was 4.378kg. The product was divided in three approximately equal portions in Pyrex dishes and dried in a fan oven at 80°C. After 2 hours a sample was taken from each tray and water analysed by decomposition to lanthanum oxide as described above. These figures were used to calculate the weight loss needed to give material of the required composition. The time course of the drying process is shown below.

Time (hours)	mol H <sub>2</sub> O/La		
	Dish 1	Dish 2	Dish 3
2	21.3	22.1	20.4
5.5	12.3	13.2	12.2
9	7.9	8.0	7.6
11.5	6.9	7.0	6.6
17	4.9	5.1	4.6
18.5	4.6	4.8	4.2
19.5	4.4	4.6	4.1
20	4.3	4.6	4.0

Samples were taken from each dish, combined and analysed. The following results were obtained:

	Found	Calculation for $\text{La}_2(\text{CO}_3)_3 \cdot 4\text{H}_2\text{O}$
% La (gravimetric)	52.38%	52.4%
carbonate (titration)	5.76mol/g	5.66mol/g
$\text{H}_2\text{O}$ (NMR)	13.06%	13.59%

5

The XRD analysis for lanthanum carbonate  $4\text{H}_2\text{O}$  prepared by the method of Example 2 is illustrated in Figure 3.

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Figure 4 illustrates the XRD of lanthanum carbonate  $8.8\text{H}_2\text{O}$  and it is evident that it has a different crystalline structure from lanthanum carbonate  $4\text{H}_2\text{O}$  prepared by the method of Example 2. The XRD analysis of lanthanum carbonate  $4\text{H}_2\text{O}$  prepared by the method of Example 1 was similar to the XRD analysis of lanthanum carbonate  $4\text{H}_2\text{O}$  prepared by the method of Example 2.

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20

Pharmaceutical compositions for oral administration according to the invention may be formulated and manufactured using methods well known in the art. Suitable diluents or carriers are also well known. The compositions may desirably be in a dosage form, to provide a single daily dose, or a number of sub-daily dosages. Conventional pharmacological methods may be used to ascertain suitable dose levels. The level of phosphate in the food that an individual ingests is important. Daily dosages are indicated to be in the range 0.1 to 50g, preferably about 0.5 to 15g. Suitable forms for oral administration include solid forms such as tablets, capsules and dragees and liquid forms such as suspensions or syrups. In addition to diluents and carriers, it is conventional in the formulation of oral preparations to include non-active

ingredients such as thickeners, taste-improving components and colouring agents. The said carbonate may also be coated or treated to provide delayed-release forms. Preferably, the required daily dosage is given in tablet form, *eg* chewable tablet form, to be taken with meals. A suitable daily dosage of about 2g for 70kg man, should be compared with a daily dosage of 20g for a commercial calcium-based phosphate binding composition.

To demonstrate that the lanthanum carbonate of the invention (or lanthanum phosphate formed after binding to phosphate in the gut) is fully excreted and does not pass out of the gut into the circulation system when given orally, three rats were dosed with 20mg/kg of  $\text{La}_2(\text{CO}_3)_3 \cdot 4\text{H}_2\text{O}$  (Sample 5) and kept in metabolic cages where faeces and urine could be collected. The results are shown in Table 2 below.

Animal No.	Time (hours)	% La Recovered
1	24	103.2
1	48	0.1
1	72	<0.2
1	Total	103.3
2	24	75.3
2	48	23
2	72	1.2
2	Total	99.5

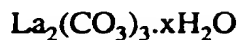
Animal No	Time (hours)	%La Recovered
3	24	93.8
3	48	10
3	72	0.1
3	Total	103.8

It can be seen that after 72 hours, all of the lanthanum has been excreted. In the urine samples, the amount of lanthanum was below detection limits. After the test, the rats were sacrificed, and kidney, liver and femur were analysed for lanthanum. In all cases, the amount of lanthanum was below 0.1ppm.

**CLAIMS**

1. A pharmaceutical composition for the treatment of hyperphosphataemia, comprising lanthanum carbonate of formula

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where x has a value from 3 to 6, in admixture or association with a pharmaceutically acceptable diluent or carrier.

10

2. A composition according to claim 1, wherein in the lanthanum carbonate, x has a value from 3.5 to 5.

3. A composition according to claim 2, wherein in the lanthanum carbonate, x has a value from 3.8 to 4.5.

15

4. A composition according to any one of claims 1 to 3, in a form suitable for oral administration.

5. A composition according to any one of claims 1 to 4 in unit dosage form to provide from 0.1 to 20g/day.

20

6. The use of lanthanum carbonate as defined in any one of claims 1 to 3, for the preparation of a medicament for the treatment of hyperphosphataemia by administration into the gastrointestinal tract.

7. A process for the preparation of lanthanum carbonate as defined in any one of claims 1 to 3 which comprises the steps of:

5 (i) reacting lanthanum oxide with an acid which gives a soluble salt of lanthanum;

(ii) reacting a solution of the thus obtained lanthanum salt with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and

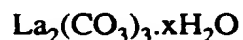
(iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

10 8. A process as claimed in claim 7 wherein the acid is nitric acid or hydrochloric acid.

15 9. A process as claimed in claim 7 or 8 wherein the alkali metal carbonate is sodium carbonate.

10. Lanthanum carbonate prepared according to the process of any of claims 7, 8 or 9.

20 11. Lanthanum carbonate of the formula



where x has a value from 3 to 6.

7. A process for the preparation of lanthanum carbonate as defined in any one of claims 1 to 3 which comprises the steps of:

(i) reacting lanthanum oxide with hydrochloric acid to obtain lanthanum chloride;

(ii) reacting a solution of the thus obtained lanthanum chloride with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and

(iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

8. A process as claimed in claim 7 wherein the alkali metal carbonate is sodium carbonate.

9. Lanthanum carbonate prepared according to the process of claim 7 or 8.

## INTERNATIONAL SEARCH REPORT

 National Application No  
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 A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 A61K33/24

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 C01F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 011, no. 371 (C-462), 3 December 1987 & JP,A,62 145024 (ASAHI CHEM IND CO LTD), 29 June 1987, cited in the application see abstract ---	1-11
X	JOURNAL OF THE LESS-COMMON METALS, vol. 167, no. 2, 1 January 1991, pages 223-232, XP000202645 NAOHISA YANAGIHARA ET AL: "SYNTHESIS OF LANTHANIDE CARBONATES" see page 226; table 2 --- -/--	11

☒ Further documents are listed in the continuation of box C..

☐ Patent family members are listed in annex.

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 107, no. 26, 28 December 1987 Columbus, Ohio, US; abstract no. 249009, MINEELY, PATRICK J.; TARIQ, SHABBIR A.: "Molten potassium pyrosulfate: reactions of lanthanum metal and six of its compounds" XP002010788 see abstract & AUST. J. CHEM. (1987), 40(7), 1309-14, ---	11
X	CHEMICAL ABSTRACTS, vol. 104, no. 26, 30 June 1986 Columbus, Ohio, US; abstract no. 236218, MZAREULISHVILI, N. V.; NATIDZE, V. P.: " Study of interaction of lanthanum nitrate with alkali metal and ammonium carbonates" XP002010789 see abstract & SOOBASHCH. AKAD. NAUK GRUZ. SSR (1986), 121(1), 81-4, ---	11
X	CHEMICAL ABSTRACTS, vol. 87, no. 20, 14 November 1977 Columbus, Ohio, US; abstract no. 161013, ODA, TOSHIYUKI: "Studies on the crystal water of lanthanum carbonates" XP002010790 see abstract & OITA DAIGAKU KYOIKUGAKUBU KENKYU KIYO, SHIZEN KAGAKU (1975), 4(5), 1-6, ---	11
X	CHEMICAL ABSTRACTS, vol. 87, no. 18, 31 October 1977 Columbus, Ohio, US; abstract no. 142122, KARAPET'YANTS, M. KH.; MAIER, A. I.; BAS'KOVA, N. A.: "Standard heats of formation of rare earth element and yttrium carbonates" XP002010791 see abstract & IZV. AKAD. NAUK SSSR, NEORG. MATER. (1977), 13(7), 1279-81, -----	11

**PHARMACEUTICAL COMPOSITION AND METHOD**

**Abstract of the Invention**

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Selected lanthanum carbonate hydrates may be administered into the gastrointestinal tract, to treat hyperphosphataemia in patients with renal failure.